Therapeutic Goods Administration consultation: Expedited pathways for prescription medicines

Criteria and designation process

Submission from the Clinical Oncology Society of Australia and Cancer Council Australia

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The **Clinical Oncology Society of Australia (COSA)** is the peak national body representing health professionals from all disciplines whose work involves the care of cancer patients.

Cancer Council is Australia's peak national non-government cancer control organisation and advises the Australian Government and other bodies on evidence-based practices and policies to help prevent, detect and treat cancer.

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Research informing cancer treatment is constantly evolving. The current regulatory system is not sufficiently sensitive to assess the complexity of many emerging cancer treatments, particularly for medicines intended to treat small patient populations or when traditional treatment methods have been exhausted. The proposed improvements to the Orphan Drug Program, and the introduction of expedited review pathways, demonstrate that the TGA recognises the benefit of improving access to products which demonstrate substantial benefit to all Australian consumers.

Expedited approval, in certain circumstances, through the application of transparent criteria for accelerated assessment of promising new drugs, should benefit cancer patients who are currently disadvantaged by the system. At a broad level, the reforms have significant potential but detail of how these pathways will be implemented, selection criteria, conditions of the designation, and post-registration surveillance will provide a better sense of how the expedited pathways will address current inequities in the access to treatment. Cancer Council and COSA welcome the opportunity to review the consultation paper. We note that while both pathways, Priority Review and Provisional Approval, are being discussed in this consultation, there will be further consultation on the details of the Provisional Approval pathway in 2017, which we intend to review.

a. Principles for TGA's expedited pathways

Comment on the principles for TGA's expedited pathways:

The principles guiding the development of the expedited pathways for medicines and medical devices are reasonable. The principles recognise the interests of all stakeholders including consumers, both patients and health care practitioners, government agencies and the pharmaceutical industry.

The first principle is the most important. There is increasing demand from health care practitioners and consumers for improved translation of research outcomes into market available medicines, and an expedited approval program would provide patients the opportunity to gain access earlier to effective new medicines. Therefore, the regulatory system itself must demonstrate a capacity to appropriately balance the benefits of early access to promising new treatments with any potential risk to the consumer[i]. The approval process must be responsive and sufficiently rapid to support patients, who are likely to benefit from treatment, to receive the medicine without lengthy delay.

An additional principle could be considered in recognition of the overall purpose of the program, such as 'Decisions must be informed by evidence of safety and efficacy related to the potential benefit applicable to the relevant pathway'.

To improve the program's benefit, the TGA registration process must be equipped to work in parallel with the review of a product's application to the Pharmaceutical Benefits Advisory Committee (PBAC). This would support the timely introduction of the therapies approved through an expedited pathway onto the Pharmaceutical Benefits Scheme (PBS).The process must also link in with the Orphan Drug Program.

b. Eligibility for the expedited pathways

Do the proposed criteria for Priority Review and Provisional Approval address the objectives of the expedited pathways?

Yes, the criteria for Priority Review and Provisional Approval address the objectives of the expedited pathways and are consistent with equivalent programs in comparable countries.

The criteria supports the program's objectives to achieve earlier access to novel prescription medicines that address unmet clinical needs for Australian consumers; increased alignment with other overseas regulators and, for the most part, provides timely and flexible registration processes for sponsors.

Regarding the treatment of cancer, these pathways would be most beneficial for bringing products to market for conditions with small patient cohorts, cancers presenting at a late stage, and where a registered product is effective in one type of cancer and indicates a high probability of effectiveness in another cancer group, such as immunotherapy products. Currently, some sponsors do not submit an application to register products with the TGA as the costs of collecting the required level of evidence to support their application may be deemed excessive in relation to the potential return, especially for less common conditions. Provisional Approval, or the review of clinical indicators other than overall survival, would support the introduction of effective products to these populations. The TGA will make a decision whether to register a product that has received Provisional Approval designation on

the basis of early efficacy and safety data from surrogate endpoints or other relevant data, rather than phase three clinical trials.

As stated in our joint submission to the *Medicines and Medical Devices review*[ii], there is increasing consumer demand for early access to novel therapies and sustainable access to effective treatment, especially for medicines and medical devices that are used to treat conditions where there is significant unmet clinical need; used to treat serious or life threatening conditions or; represent major advancement in treatment. All three points are included in the criteria above, and in addition to our suggestion, the TGA has included the requirement that all three-selection criteria must be met to achieve designation. It is important to maintain rigour in the assessment of safety and efficacy however; the system must be adaptive to changing methods of treatment and flexible enough to consider the patient context.

What other considerations may need to be included?

As emphasised in our joint submission to the 2015 *Senate inquiry into the availability of new, innovative and specialist cancer drugs in Australia*[iii], there is a case for the TGA (and PBAC) to consider surrogate endpoints in addition to overall survival which demonstrate clinical benefit, for the earlier introduction of products to market. This registration would be approved with pre-determined provisions around its ongoing availability through a process of post-market surveillance. There is some evidence that surrogate endpoints (such as progression-free survival) can be a precursor to subsequent clinical benefits measurable in increased quality of life years[iv].

The assessment of major therapeutic advantage must consider the impact of treatment toxicity as reported in the review of its clinical efficacy. Quality of life measures, such as a reduction in disability adjusted life years, for someone diagnosed or living with cancer can be a significant and meaningful treatment outcome for many patients.

c. Designation for the expedited pathways

Is the proposed process and timing of the designation steps appropriate?

Yes, the sequence of the process is logical and is closely aligned with overseas regulators that offer accelerated assessment processes.

What other considerations may need to be taken into account in implementing the proposed designation process?

The introduction of expedited review pathways will require additional resourcing and will impact on current TGA meeting schedules and require increased input from clinical and scientific experts. As the TGA and this program are financed through a cost recovery model, the financial impact of the increase in applications should be appropriately recovered through application fees. The program requires flexibility to meet demand to ensure the objectives of the expedited review program are being met. The coordination of processes and committees/advisors involved in the decision making process is critical to ensuring reviews are conducted within the target timeframes specified.

If Provisional Approval designation is granted and the sponsor subsequently applies to register the product with the TGA, the conditions of the registration must be clearly outlined. The TGA must implement a rigorous evaluation of the ongoing safety and efficacy of the products

through quality data collection and outcome reporting, and the sponsor must meet these conditions. We recognise the TGA's intention to request input on the details of the Provisional Approval pathway in early 2017. We look forward to reviewing and responding to that consultation, as it is critical to establish the post-market evaluation process prior to the implementation of expedited review pathways.

d. Duration of designation:

Should there be *three-month* limit on the duration for the designation for Priority Review and Provisional Approval? If not, please provide reasons and suggest what could be an alternative time period.

We support a three-month window from the acknowledgement of the approved designation to the submission of a complete application for the TGA's consideration to register the product. However, the TGA should recognise the Provisional Approval as an ongoing designation based on the ability to maintain the conditions of the designation, or until a substantial level of evidence supporting the product's clinical efficacy is produced.

Similarly to the proposed changes to the Orphan Drug Program[v], introducing a dedicated timeframe from designation approval to application for registration is critical to ensure decisions are made on current evidence. The TGA would have the authority to cancel a designation prior to application to the TGA for registration if new evidence emerges that no longer supports the designation.

e. Publication of TGA decisions:

Should we publish the outcomes of applications for Priority Review and/or Provisional Approval designation?

Yes, the TGA publishes the Australian Public Assessment Reports (AusPAR) for prescription medicines which have applied through the regular TGA registration process. We recommended that this level of public reporting remains in place to support consistency, and continues to promote transparency, for the reporting of outcomes from applications for designation status considered under Priority Review and Provisional Approval.

Australian Public Assessment Reports for Prescription Medicines provide information about the evaluation of a prescription medicine and considerations that led the TGA to approve or not approve an application. A new AusPAR is created for all new chemical entities and provides a consistent format for reporting[vi].

Consumers should have the ability to know which therapeutic products are being considered by the TGA, and sponsors of other therapeutic products should be able to consider their applications against the outcomes of other reviews. Public and industry groups actively monitor progress of applications to the TGA.

Should publication of both 'eligible' and 'ineligible' designation decisions occur?

Yes, the TGA must be transparent in their assessment of applications under the expedited review pathways. If ineligible, the TGA must allow the sponsor 90 days to consider the

publication of the outcome, as currently offered through the regular registration process,. AusPARs are available for all prescription listings from 2009 and include rejected submissions if passed the 90-day internal review date[vii]. Within this review period sponsors have the opportunity to request that any information classified as commercial in confidence remains protected.

Should we publish whether a medicine has been registered through one of the expedited pathways?

Yes, this should be consistent with the AusPAR.

If so, how much detail should be published and when should TGA decisions be published?

The TGA and European Medicines Association recently co-wrote a paper on their commitment to transparency by publishing information relating to their evaluation of medicines via public assessment reports[viii]. Such commitment must be reflected through all TGA evaluation processes and supports multiple principles underpinning the expedited review program.

For registrations approved under Priority Review reporting the TGA should provide a full AusPAR report as per registrations made through the regular registration process. The TGA would be required to publish different information on products registered with Provisional Approval designation to encompass conditional criteria. The public reporting of these conditions promotes transparency in decision-making, as the product must report ongoing clinical data collection and evaluation of the product's safety, quality and efficacy in practice. Decisions should be published in line with current TGA publication dates, including the 90-day allowance for sponsors of non-approved products to review the public report prior to wider availability. Publicly available information should be provided as soon as it is practically possible.

f. Other considerations:

What other key issues should be considered in developing the Priority Review and Provisional Approval Pathways?

i. Provisional Approval designation:

As noted, we are aware of the intension of the TGA to request public consultation on the details of the Provisional Approval pathway in early 2017 however, we raise the following issues which we will explore in our submission to that consultation. It is critical that the conditions of approval, and the TGA's process for the ongoing evaluation of listed products under the Provisional Approval designation, are considered and implemented alongside the introduction of the TGA expedited review processes.

- Details of the conditions of registration under the Provisional Approval designation, including for how long a designation is assigned once the product is listed on the Australian Register of Therapeutic Goods;
- Details of the TGA's process for the ongoing review of registrations under the Provisional Approval designation, and what criteria is applied in the evaluation of the maintenance of the designation, and the frequency of these reviews;
- Ensuring accurate and relevant data is collected and reported by sponsors of products registered under the Provisional Approval designation;

- Consider whether registered products on Provisional Approval can apply to the PBAC to be considered for subsidisation;
- Recognise the impact on downstream processes, most significantly the impact on a products ability to be considered for subsidy by the PBAC. Without affordable pricing of these products, access may be limited to individuals and hospital pharmacies that can afford to pay the potentially high costs for these therapies. Not only does this pose a further delay or barrier to access, but also skews the data collected as part of the condition of approval of products brought to market. The process needs to ensure that there is a commitment from the sponsor to set a reasonable price, apply to the PBAC (if the Provisional Approval designation allows) and capture data that is representative of the patient group.

ii. Cost associated with an expedited review:

The consultation paper did not provide details of the fees associated with a product seeking registration through the Provisional Approval pathway. Our understanding is that there would be fees associated with the initial designation process, the standard TGA registration process, and the annual charge for ongoing review of Provisional Approval designation. We would encourage the TGA to consider applying fees that are appropriate to cover the costs associated with the all components of the assessment pathway, but also that this does not prohibit the sponsor to seek earlier registration of these products. The earlier introduction to market is an incentive for sponsors but this should be balanced with reasonable and transparent costs associated with registration depending on the particular expedited pathway.

iii. Evaluation of the program:

There is no detail within the consultation paper indicating the TGA's intention to evaluate the expedited pathways for prescription medicines program once it is implemented. We recommend that the TGA consider how the program would be evaluated to ensure it meets stakeholder demands, delivers on its purpose and objectives, and ensures appropriate resourcing is allocated to activities of the expedited review pathway.

iv. Input from TGA Advisory Committees:

Existing TGA Advisory Committees, who are tasked with providing expert input to the review of applications to both the Priority Review and Provisional Approval pathways, must be able to support the flexible and adaptive nature of a fast paced expedited review process. Their commitment to the expedited pathways requires consideration of their resourcing, review timeframes, and flexibility to ensure the timeliness, as outlined by the proposed process, can be met.

v. Evaluation of products on the Australian Register of Therapeutic products:

We acknowledge recommendation 27 from the *Medicines and Medical Devices review*[ix] that 'the Australian Government develop a more comprehensive post-market monitoring scheme for medicines and medical devices.' This recommendation was adopted by the Australian Government. In our opinion, this recommendation which focuses on the post approval data collection for registered therapeutic products in Australia, is critical to ensure the TGA continues to provide access to safe and effective products. We look forward to reviewing and commenting on a post-market monitoring scheme for all registered products as part of a future consultation.

Conclusion:

Cancer Council and COSA welcome the TGA's exploration of expedited review processes to support the earlier introduction of medicines and medical devices, which prove promising results. Currently the options for early access for patients are inequitable, inflexible and not keeping pace with the way new medicines for cancer are being developed.

We welcome this investigation into sustainable and equitable processes for expedited review and access to effective new or breakthrough medicines for patient groups who could benefit from earlier access to novel therapies; and consider conditions around provisional approval of the drugs including consequences of not demonstrating clinical efficacy against pre-approved milestones, and implications for ongoing access for existing patients.

Fast market access does not necessarily translate into consumer access because in practice the cost of medicines could be prohibitively expensive for many patients. Hopefully this will translate into earlier PBAC approval, as the availability on the PBS is the critical element to permit broad access to high cost beneficial new drugs for Australian cancer patients.

References:

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[iv] Griebsch I, Palmer M, Fayers P, & Ellis S. Is progression-free survival associated with a better health-related quality of life in patients with lung cancer? Evidence from two randomised trials with afatinib. *British Journal of Medical Oncology* Volume 4, October 2014. Online access via http://bmjopen.bmj.com/content/4/10/e005762.long

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